



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US99/16049          (22) International Filing Date: 15 July 1999 (15.07.99)          (30) Priority Data:          60/092,982 16 July 1998 (16.07.98) US          (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application          US 60/092,982 (CIP)          Filed on 16 July 1998 (16.07.98)          (71) Applicant (for all designated States except US): MEMORIAL SLOAN-KETTERING CANCER CENTER [US/US]; 1275 York Avenue, New York, NY 10021 (US).          (72) Inventors; and          (75) Inventors/Applicants (for US only): KOLESNIKOV, Yuri [RU/US]; 38 Ridge Road, Cresskill, NJ 07626 (US). PASTERNAK, Gavril, W. [US/US]; Apartment 21M, 500 E 83rd Street, New York, NY 10021 (US).</p>	<p>(74) Agents: SONNENFELD, Kenneth, H. et al.; Morgan &amp; Finnegan, L.L.P., 345 Park Avenue, New York, NY 10154 (US).          (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).          Published  <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC AND AN NMDA ANTAGONIST</p>		
<p>(57) Abstract</p> <p>A topical opioid paradigm was developed to determine analgesic peripheral effects of morphine. Topical morphine as well as peptides such as [D-Ala<sup>2</sup>,MePhe<sup>4</sup>,Gly(ol)<sup>5</sup>]enkephalin (DAMGO) produced a potent, dose-dependent analgesia using the radiant heat tailflick assay. The topical drugs potentiated systemic agents, similar to the previously established synergy between peripheral and central sites of action. Local tolerance was rapidly produced by repeated daily topical exposure to morphine. Topical morphine tolerance was effectively blocked by the N-Methyl-D-Aspartate (NMDA) receptors antagonist MK801 and ketamine given either systemically or topically. NMDA receptor antagonists reversed pre-existing morphine tolerance. The activity of topical NMDA antagonists to block local morphine tolerance suggests that peripheral NMDA receptors mediate topical morphine tolerance. Morphine was cross tolerant to [D-Ala<sup>2</sup>,MePhe<sup>4</sup>,Gly(ol)<sup>5</sup>]enkephalin (DAMGO), but not to morphine-6<math>\beta</math>-glucuronide, implying different mechanisms of action. These observations have great importance in the design and use of opioids clinically. Topical pharmaceutical compositions comprising an analgesic that functions through an opiate receptor and an NMDA receptor antagonist for producing analgesia without inducing tolerance are described.</p>		

° **TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC AND AN NMDA  
ANTAGONIST**

5 This application claims priority to provisional U.S. application Serial  
No. 60/092,982 filed July 16, 1998 which is incorporated herein by reference in its  
entirety.

This invention was made with government support under Grant  
Number DA07242, DA00220 and CA08748 awarded by The National Institutes of  
10 Health. The U.S. government has certain rights in the invention.

**FIELD OF THE INVENTION**

The invention is directed to topical pharmaceutical compositions of  
an N-methyl-D-aspartate receptor antagonist alone or in combination with an  
15 analgesic that functions through an opiate receptor for peripheral analgesia and uses  
of the topical pharmaceutical compositions for treatment of pain, with no/or  
minimal tolerance development to the analgesic.

**BACKGROUND OF THE INVENTION**

20 Morphine is a potent mu opioid receptor agonist with important  
central sites of action (Reisine and Pasternak, 1996). Peripheral mechanisms also  
have been reported and their importance is becoming increasingly appreciated (Stein  
*et al.*, 1995; Barber and Gottschlich, 1992; Joris *et al.*, 1987; Junien and Wettstein,  
1992). Peripheral analgesics have a number of potential advantages in the clinical  
25 treatment of pain, particularly the limitation of side-effects such as constipation and  
sedation which are typically seen with systemic administration. Given locally into  
the tail, morphine and other opioids are effective analgesics, working either alone  
peripherally or synergistically at central sites (Kolesnikov *et al.*, 1996). In many  
30 respects, these studies are similar to clinical investigations (Stein, 1993; Dahl *et al.*,  
1990; Dalsgaard *et al.*, 1994; Heard *et al.*, 1992; Joris *et al.*, 1987; Khoury *et al.*,  
1992; Mays *et al.*, 1987; Raja *et al.*, 1992). Peripheral mechanisms also have been  
implicated in systemic morphine tolerance (Kolesnikov *et al.*, 1996). Early studies  
35 reported that systemic morphine tolerance does not alter the sensitivity to morphine  
given either spinally or supraspinally (Roerig *et al.*, 1984). Although we also found

**BRIEF DESCRIPTION OF THE FIGURES****Fig. 1a and 1b: Topical opioid analgesia in the mouse**

1a) Groups of mice received a 2 min topical exposure to morphine (15 mM; n=20), DAMGO (2 mM; n=10) or M6G (20 mM; n=10) and were tested in the tailflick assay.

1b) Dose-response curves were generated for each of the designated compounds applied topically for 1 min, as described in Methods. Each dose of drug had at least 10 mice/group.

**Fig. 2a and 2b: Effects of opioid antagonists on topical Mu analgesia**

2a) Groups of mice ( $n \geq 10$ ) received either morphine (15 mM), DAMGO (2 mM) or M6G (20 mM) topically for 1 min alone or with naloxone (1 mg/kg, s.c.) injected subcutaneously on the back 20 min prior to the analgesic agonists. Naloxone, a Mu receptor antagonist, significantly reduced the responses for all agonists.

2b) Groups of mice ( $n \geq 10$ ) received either morphine (15 mM), DAMGO (2 mM) or M6G (20 mM) topically for 1 min alone or with 3-methoxynaltrexone (3-MeONTx; 0.25 mg/kg, s.c.) injected subcutaneously on the back 20 min prior to the agonists. 3-MeONTx significantly lowered the response only for M6G.

**Fig. 3a and 3b: Interactions between topical and either systemic or spinal morphine**

3a) Groups of mice ( $n \geq 10$ ) received topical morphine (15 mM; 2 min) alone, or with spinal (100 ng, i.t.) or systemic (1 mg/kg, s.c.) morphine. The spinal morphine dose alone had no observable action and the systemic dose produced only a 10% response. At 30 min, when the response to topical drug alone was lost, the responses of the combinations were significantly greater.

0.01). The combination of morphine with either systemic or topical MK801 remained essentially unchanged for five days.

6b) Groups of mice ( $n \geq 10$ ) received topical morphine (15 mM; 1 min) alone, topical MK801 alone (3 mM) or topical morphine (15 mM) with topical MK801 at the indicated concentration (0.15, 0.3 or 3 mM). After three days, the response to morphine alone was lost ( $p < 0.01$ ). The two higher MK801 doses prevented the loss of responsiveness ( $p < 0.01$ ) while the lowest doses gave an intermediate response.

6c) Groups of mice ( $n \geq 10$ ) received topical morphine (15 mM; 1 min) alone for three days. Starting on the fourth day, they received topical morphine with topical MK801 at either 0.3 or 3 mM. Coadministration of topical MK801 with topical morphine reversed the previously established tolerance ( $p < 0.01$ ).

#### **Figure 7a and b: Effect of ketamine on topical morphine tolerance**

7a: Groups of mice ( $n=20$ ) were treated topically once daily for 3 days with morphine (15mM) alone (closed circles) or both morphine with ketamine at 3.6mM (triangles) or 36mM (open circles). Ketamine alone (36mM) did not produce significant analgesia in this model. After three days, the response to morphine alone was lost ( $p<0.001$ ). The lower ketamine dose (3.6mM) significantly lessened the loss of morphine analgesic response after three days ( $p<0.05$ ). The higher ketamine dose (36mM) prevented tolerance up to six days ( $p<0.0001$ ).

7b. Groups of mice ( $n=20$ ) received topical morphine (15mM) alone (closed circles) for two days. Starting on the day 3, the two groups of mice received daily doses of morphine in conjunction with either ketamine at either 3.6 (triangles) or 36mM (squares) through day 6. The higher ketamine dose (36mM) completely restored morphine analgesia ( $p<0.0001$ ).

#### **DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides a topical pharmaceutical composition comprising of at least one N-methyl-D-aspartate (NMDA) receptor antagonist alone

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Glycol)<sup>5</sup>]enkephalin (DAMGO), propoxyphene, buprenorphine, oxycodone, hydromorphone, hydromorphone, fentanyl, sufentanil, pentazocine, nalbuphine, nalorphine, heroin, levorphanol, levallorphan, methadone, meperidine, cocaine, dihydrocodeine, hydrocodone, nalmefene, naloxone, naltrexone, butorphanol, and the pharmaceutically acceptable salts and the like.

Optionally, the topical pharmaceutical composition of the present invention may further comprise a local anesthetic including but not limited to lidocaine, bupivacaine, meprivacaine, ropivacaine, tetracaine, benzocaine and the like.

As used herein, a mammal that may benefit from the methods of treatment of the present invention is any warm-blooded animal in need of treatment for pain. Mammals include but are not limited to humans, primates, dogs, cats, rodents, horses, cattle, sheep, and the like. The analgesic is provided to a mammal in need of relief from pain. The pain may be an acute or chronic pain. Diseases or conditions which may necessitate analgesia include but are not limited to pain associated with trauma, amputation, neuropathy, fibromyalgia, burns, abrasions, infections, lacerations, incisions and the like.

This invention provides for attenuating or preventing the development of tolerance associated with the administration of narcotic analgesics. Accordingly, NMDA receptor antagonists may be administered in amounts which are effective for either attenuating or preventing tolerance development. As used herein, the term tolerance preventing, tolerance-inhibiting or tolerance-reversing dose is an amount of an NMDA receptor antagonist effective to maintain and/or restore, or at least partially restore, the analgesic effect of the narcotic analgesic.

In a method of providing peripheral analgesia to a mammal, a tolerance-attenuating or preventing dose of at least one NMDA receptor antagonist is administered topically prior to, concurrently or following topical administration of at least one analgesic that functions through an opiate receptor.

In one embodiment of the method of providing analgesia to a mammal, a tolerance-attenuating or inhibiting dose of the NMDA receptor

or more of the following - petrolatum, lanoline, polyethylene glycols, bee wax, mineral oil, diluents, such as water and alcohol, and emulsifiers and stabilizers.

Aqueous suspensions can contain the composition in admixture with pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, e.g., heptadecaethyleneoxycetanol, or condensation products ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monooleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylenes sorbitan monooleate. Such aqueous suspensions can also contain one or more preservatives, e.g., ethyl or n-propyl-p-hydroxy benzoate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the composition in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

The composition of this invention or either of its principal active ingredients can be provided in sustained release dosage formulations as are known in the art.

A topical formulation of the present invention delivers a therapeutic effect on the peripheral opiate receptors and is not required to deliver the active ingredients in the topical formulation to central (brain and spinal cord) opiate receptors. The topical formulations of the present invention provides local delivery of the active ingredients and is not required to provide systemic delivery of the active ingredients in the formulation in the treated mammals.

analgesic in a pharmaceutical composition for use in the combination analgesic therapy is in range as so to provide about 0.1 to about 0.2 mg/kg body weight. In the case of intrathecal administration of an analgesic, in combination with a topical analgesic, the concentration of the intrathecal analgesic is in a range of about 1 to about 5 mg. The therapy may be supplemented by administration of a tolerance-attenuating or tolerance-preventing dose of at least one topical NMDA receptor antagonist. The topical NMDA receptor antagonist may be provided in a concentration range of about 0.1% to about 5% by weight of the formulation.

In one embodiment of a method of providing analgesia to a mammal, topical morphine is administered prior to, concurrently or following systemic or intrathecal administration of morphine.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and therefore such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments.

All references and patents referred to are incorporated herein by reference.

### **Example 1**

#### **Materials and Methods**

Male Crl:CD-1(ICR)BR mice (25-30 g; Charles River Breeding Laboratories, Bloomington, MA) were maintained on 12 -h light/dark cycle with food and water available ad libitum. Mice were housed in groups of five until testing. [<sup>125</sup>I]NaI (1680 Ci/mmol) was purchased from New England Nuclear (Boston, MA). Morphine, morphine-6 $\beta$ -glucuronide (M6G) and [D-Ala<sup>2</sup>,MePhe<sup>4</sup>,Gly(ol)<sup>5</sup>]enkephalin( DAMGO) were generously provided by the Research Technologies Branch of National Institute on Drug Abuse (Rockville, MD). MK801 was purchased from Research Biochemicals, Inc. (Natick, MA).

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and either morphine or DAMGO. The reaction terminated with sodium metabisulfite after 1 minute and the radiolabeled opioid separated from unreacted  $N^{125}I$  by a C18-reverse phase SepPak (Chien *et al.*, 1997). The radiolabeled compounds were not further separated from the non-iodinated precursors.

### Example 2

#### **Topical morphine and DAMGO analgesia**

Prior studies from our group demonstrated a potent local analgesic activity of morphine administered subcutaneously in the tail (Kolesnikov *et al.*, 1996). Morphine also was a potent analgesic when applied topically. The analgesic response to a morphine solution (7.5 mM) progressively increased over time, going from only 25% after 30 seconds to 50% by one minute and 80% after 2 min (data not shown). The onset of the response was quite rapid. Analgesia was detectable within one minute after removal of the tail from the opioid solution, the shortest time tested (Fig. 1a). However, the duration of the morphine response was relatively brief, typically lasting less than 30 min. Using a fixed exposure time, morphine produced a dose-dependent effect (Fig 1b; Table 1). Similar results were observed with DMSO solutions of the mu opioid peptide DAMGO, which was over 5-fold more potent (Fig1b; Table 1).

**Table 1: Analgesic activity of topical opioids in CD-1 mice**

Opioids	ED <sub>50</sub> (95%CL)	Relative potency
Morphine	8.3 mM (4-13)	1
M6G	9.3 mM (7-14)	0.9
DAMGO	1.6 mM ( 1-2.5)	5

Analgesic ED<sub>50</sub> values with 95% confidence limits were determined using at least three doses of drug in groups of mice (n=10-20/dose) in the tailflick assay. All drugs were administered topically for 1 min, as described in Methods. The ratio of M6G and DAMGO was determined against morphine.



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The distal part of the tail (4-4.5 cm) was immersed in [ $^{125}$ I]-labeled morphine or DAMGO (100  $\mu$ Ci/ml) in DMSO and exposed for 3 min. Brain, spinal cord, blood samples, as well as segments from the exposed and unexposed portions of the tail were obtained within 5 min of exposure, weighed and counted directly in a Packard 5500 Gamma Spectrometer. The unexposed tail was less than a 1 cm from the exposed region. Radioactivity was expressed in cpm per gram tissue (cpm/g). Results are the means  $\pm$  s.e.m. of three animals for each radiolabeled drug.

### **Example 3**

#### **Topical morphine-6 $\beta$ -glucuronide analgesia**

Morphine-6 $\beta$ -glucuronide (M6G) administered locally by subcutaneous injection in the tail was analgesic, but it had a ceiling effect of 30% with doses of 10 or 30  $\mu$ g (data not shown). In the topical paradigm, M6G yielded a full analgesic response with a peak effect immediately after removal from the solution (Fig. 1a) and a potency similar to that of morphine (Fig 1b; Table 1). As with morphine, proximal tail segments did not display analgesia and the M6G response was readily reversed by systemic naloxone (Fig. 2a). The duration of M6G action following topical administration was similar to that of DAMGO and longer than those of morphine (Fig. 1a). The M6G-selective antagonist 3-methoxynaltrexone (3MeONtx) (Brown *et al.*, 1997) also significantly lowered the M6G response (Fig 2b). In contrast, the same 3MeONtx dose was inactive against the analgesic actions of morphine or DAMGO (Fig 2b). In addition to supporting the selectivity of 3MeONtx for the M6G receptors, these observations strongly supported the presence of functional peripheral M6G receptors.

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following the treatments, at which point the topical morphine had only a limited (15%) response.

Topical morphine potentiated the analgesic potency of systemic morphine almost 7-fold, even though it had no activity alone at the time point examined (30 min). Topical morphine also enhanced the potency of intrathecal morphine almost 12-fold. Thus, these results support the earlier suggestions of potentiation between peripheral and central morphine analgesic systems.

### Example 5

#### **Peripheral morphine tolerance**

Peripheral systems are important in the production of tolerance following systemic administration of morphine (Kolesnikov *et al.*, 1996). The tail immersion approach permits repeated local administration of drug without tissue damage, facilitating the study of peripheral morphine tolerance. Daily topical morphine (15 mM) produced profound tolerance by the third day (Fig. 4), shifting morphine's ED<sub>50</sub> value over 9-fold (Table 4). Topical tolerance developed more rapidly and to a greater extent than that seen with daily systemic drug, where 5 days of treatment only shifted the morphine dose-response approximately 2-fold.

**Table 4: Tolerance to systemic and topical morphine**

Morphine Treatment	ED <sub>50</sub> ( 95% confidence limits )		Ratio
	Naïve	Tolerant	
Systemic	4.3 mg/kg (2.4-5.9)	8.7 mg/kg (5.4, 9.7)	2
Topical	8.3 mM (4.1-10.2)	78 mM (49, 123)	9.4

Morphine ED<sub>50</sub> values following either topical or systemic administration were determined in naïve mice and in groups of mice which had

### by the NMDA Antagonist, Ketamine

Daily topical morphine (15mM) led to tolerance with the complete loss analgesia by the third day (Fig 7A and B). The NMDA receptor antagonist ketamine given systemically prevented the development of tolerance to topical morphine, but intrathecal ketamine was ineffective (data not shown). Topical ketamine co-administered with morphine blocked tolerance as effectively as systemic drug in a dose-dependent manner (Fig. 7A). The lower dose (3.6mM) delayed the appearance of tolerance, but the higher dose (36mM) effectively blocked tolerance. Ketamine alone had no appreciable effect in this assay.

Topical ketamine also reversed pre-established tolerance (Fig. 7B). After treating mice with a fixed concentration of topical morphine alone for three days the mice displayed no analgesia. Ketamine added to the treatment regime restored analgesic sensitivity over next three days despite the continued administration of morphine.

The ability of topical ketamine to prevent and/or reverse morphine tolerance implies a peripheral mechanism of action and is similar to the above experiment with dizocilpine (MK-801). Mechanistically, these observations are consistent with the possibility that peripheral tolerance is mediated through peripheral NMDA receptors, possibly on the same dorsal root ganglia neurons containing the opioid receptors.

### Discussion

Peripheral opioid actions are becoming increasingly important in our understanding of opioid actions, as demonstrated by the role of peripheral and central synergy in the actions of systemic morphine (Kolesnikov *et al.*, 1996). Furthermore, peripheral sites of action play a major role in the development of tolerance to systemic drug. Exploring peripheral mechanisms is not simple. Earlier studies utilized local injections into the tail to examine peripheral mechanisms. Although useful, this approach has a number of disadvantages, particularly when looking at repeated dosing. In an effort to avoid this problem, we have developed a

revealed marked potentiation of the responses beyond those expected for simple additive interactions. Thus, if topical opioids were to be used clinically, these results would suggest that they would be most effective in combination with systemic dosing. By lowering the necessary doses of systemic drug, topical opioids might greatly diminish the side-effects currently associated with opioid analgesics.

Chronic dosing with systemic morphine treatment leads to tolerance. Localizing the site of morphine tolerance has been difficult. Mice tolerant to systemic morphine show normal sensitivities to morphine given either spinally or supraspinally (Roerig *et al.*, 1984), but not peripherally (Kolesnikov *et al.*, 1996). Indeed, the 19-fold shift in the local morphine dose-response curves far exceed the shift following systemic administration. Our current studies support a role for peripheral sites in morphine tolerance. Chronic topical morphine produced tolerance very rapidly, decreasing the response to undetectable levels by three days corresponding to over a 9-fold shift in the dose-response curve. Chronic dosing with DMSO alone had no effect. The rate of development of tolerance to equianalgesic doses of systemic drug was slower and to a smaller extent, shifting the dose-response curve only 2-fold after 5 days. Mice tolerant to peripheral morphine were cross tolerant to DAMGO, but not to M6G. This lack of cross tolerance is consistent with the selective reversal of M6G analgesia by 3-MeONTx and is consistent with a unique receptor mechanism of M6G action.

N-Methyl-D-aspartate (NMDA) receptor antagonists or nitric oxide synthase (NOS) inhibitors prevent the production of morphine tolerance (Trujillo and Akil, 1994; Gutstein and Trujillo, 1993; Ben-Eliyahu *et al.*, 1992; Kolesnikov *et al.*, 1993). In view of the importance of peripheral opioid mechanisms in tolerance in these paradigms, we looked at the role of peripheral NMDA antagonists. Topical morphine tolerance was effectively blocked by MK801 given systemically or topically, but not spinally. Systemic MK801 would be expected to have access throughout the animal, including peripheral sites, while the intrathecal drug would be restricted to central sites. Likewise, topical ketamine prevented and/or reversed morphine tolerance. Thus, only treatments with access to peripheral sites were

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AMPA or KA results in pain behaviors in rats. *Neuroreport* 7:895-900.

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8. The topical pharmaceutical composition according to claim 7, wherein the local anesthetic is selected from the group consisting of lidocaine, bupivacaine, mepivacaine, ropivacaine, tetracaine and benzocaine.

5 9. A method of providing peripheral analgesia to a mammal comprising topical administration of a tolerance-attenuating or preventing dose of at least one NMDA receptor antagonist prior to, concurrently, or following topical administration of at least one analgesic that functions through an opiate receptor.

10 10. The method according to claim 9, wherein the NMDA receptor antagonist is selected from the group consisting of dextromethorphan, dextrorphan, ketamine, pyroloquinoline quinone, cis-4-(phosphonomethyl)-2-piperidine carboxylic acid, MK801, memantine, and their mixtures and  
15 pharmaceutically acceptable salts thereof.

11. The method according to claim 9, wherein the analgesic is selected from the group consisting of an opiate, an opiate derivative, an opioid, enkephalins and endorphins.  
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12. The method according to claim 11, wherein the opioid is selected from the group consisting of ethylmorphine, hydromorphone, morphine, oxymorphone, codeine, levorphanol, oxycodone, pentazocine, propoxyphene,  
25 fentanyl, sufentanil, lofentanil, morphine-6-glucuronide and buprenorphine.

13. The method according to claim 9, wherein the enkephalin is selected from the group consisting of [D-Ala<sup>2</sup>, MePhe<sup>4</sup>, Gly (ol)<sup>5</sup>] enkephalin, and endorphines.  
30

14. The method according to claim 9, wherein the NMDA receptor antagonist is administered in a dose of about 0.1% to about 5%.

15. A method of providing analgesia to a mammal with pre-existing tolerance to an analgesic comprising topical administration of an effective  
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Fig. 1a

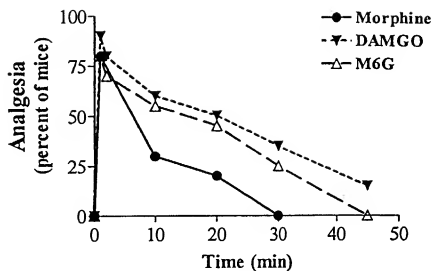
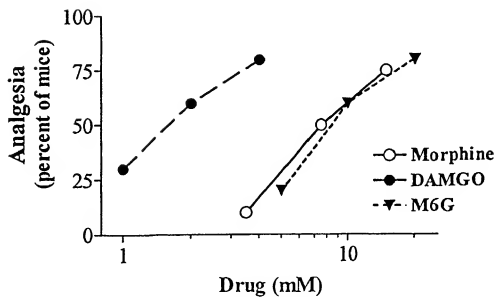


Fig. 1b





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Fig. 3a

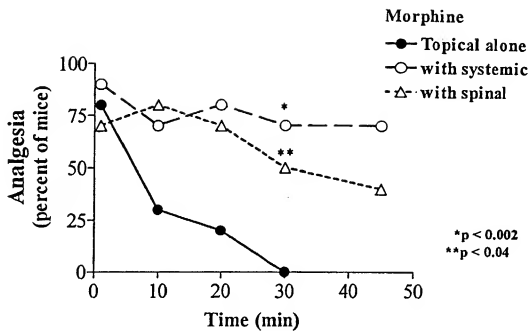
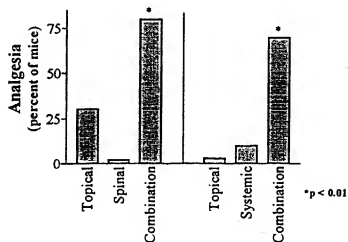


Fig. 3b



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Fig. 6a

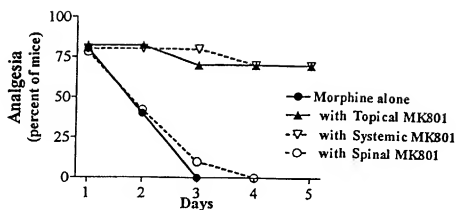


Fig. 6b

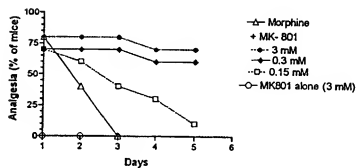
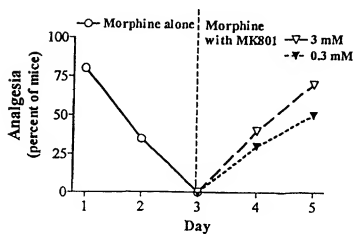


Fig. 6c



## INTERNATIONAL SEARCH REPORT

International Application No.

PL /US 99/16049

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/485 A61K31/4468 A61K31/4535 A61K38/33 A61P23/00  
 A61L29/00 A61P29/00 //(A61K31/485, 31:138), (A61K31/485,  
 31:13), (A61K31/485, 31:445), (A61K31/485, 31:485)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 31358 A (CORNELL RES FOUNDATION INC) 23 July 1998 (1998-07-23)  claims 1-5, 11 page 11, line 5-19 page 12, line 16-20 ---	1-3, 5, 7-9, 11, 12, 14-18
X	US 5 635 204 A (GEVIRTZ CLIFFORD ET AL) 3 June 1997 (1997-06-03) claims	9-12, 14, 16
Y	---	1-18
Y	WO 97 10815 A (FROME BRUCE M) 27 March 1997 (1997-03-27) abstract; claims 1, 2 ---	1-18

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

8 November 1999

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/16049

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
W0 9831358	A	23-07-1998	AU 6244898 A	07-08-1998
US 5635204	A	03-06-1997	NONE	
W0 9710815	A	27-03-1997	NONE	